The Ovarian Cancer Research Program (OCRP)
Congressionally Directed Medical Research Programs

History: The Congressionally Directed Medical Research Programs (CDMRP) were born from a powerful grassroots effort led by the breast cancer advocacy community that convinced Congress to appropriate funds for breast cancer research. This enabled a unique partnership among the public, Congress, and military. The CDMRP was created within the U.S. Army Medical Research and Materiel Command (USAMRMC) in fiscal year 1993 (FY93) to manage these funds. The CDMRP has grown to encompass multiple targeted programs and has received over $3 billion (B) in appropriations from its inception in FY93 through FY05. Funds for the CDMRP are added to the Department of Defense (DOD) budget, where support for individual programs such as the Ovarian Cancer Research Program is allocated via specific guidance from Congress.

Proposal Review Process: The CDMRP uses a two-tier review process for proposal evaluation. Both steps in this process involve dynamic interaction between scientist reviewers and nonscientific consumer reviewers. Scientific reviewers and other professionals are selected for their subject matter expertise. Consumer reviewers provide a perspective that is complementary to the scientific expertise. The first tier of evaluation is a scientific peer review of proposals against established criteria for determining scientific merit. The second tier is a programmatic review of proposals that is conducted by the Integration Panel (composed of scientists, clinicians, and consumers), compares submissions to each other, and recommends proposals for funding based on scientific merit, portfolio balance, and overall goals of the program.

Approximately 200 world-renowned scientists, clinicians, policymakers, and consumer advocates have served on the CDMRP's Integration Panels

Over 3,000 scientists, clinicians, consumer advocates, and other professionals have brought their expertise to scientific peer and programmatic review

Almost 7,000 scientists and clinicians have received awards from the CDMRP

94 scientists, clinicians, and professionals manage the CDMRP

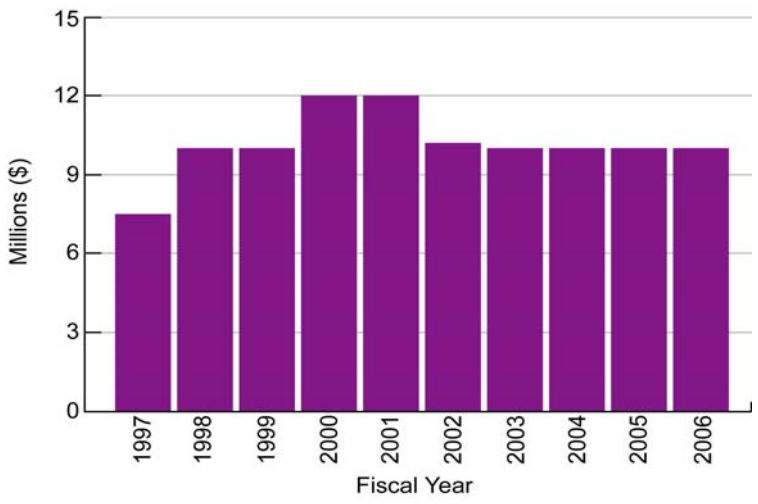
Ovarian Cancer Research Program Vision: eliminate ovarian cancer

The overall goal of the OCRP is to eliminate ovarian cancer by stimulating and supporting innovative, integrated, multidisciplinary research efforts that will lead to better understanding, detection, diagnosis, prevention, and control of ovarian cancer.

History

Efforts by ovarian cancer advocates led to a Congressional appropriation of $7.5 million (M) in fiscal year 1997 (FY97) to establish the Department of Defense (DOD) Ovarian Cancer Research Program (OCRP). As a major leader in extramural ovarian cancer research, the OCRP has managed $101.7M from FY97 to FY06 in an effort to eliminate ovarian cancer using the two-tier review model recommended by the National Academy of Sciences Institute of Medicine. This model has received high praise from the scientific community, advocacy groups, and Congress. Key initiatives of the OCRP include supporting critical research resources, funding innovative research, and bringing talented investigators into the ovarian cancer field.

OCRP Appropriations



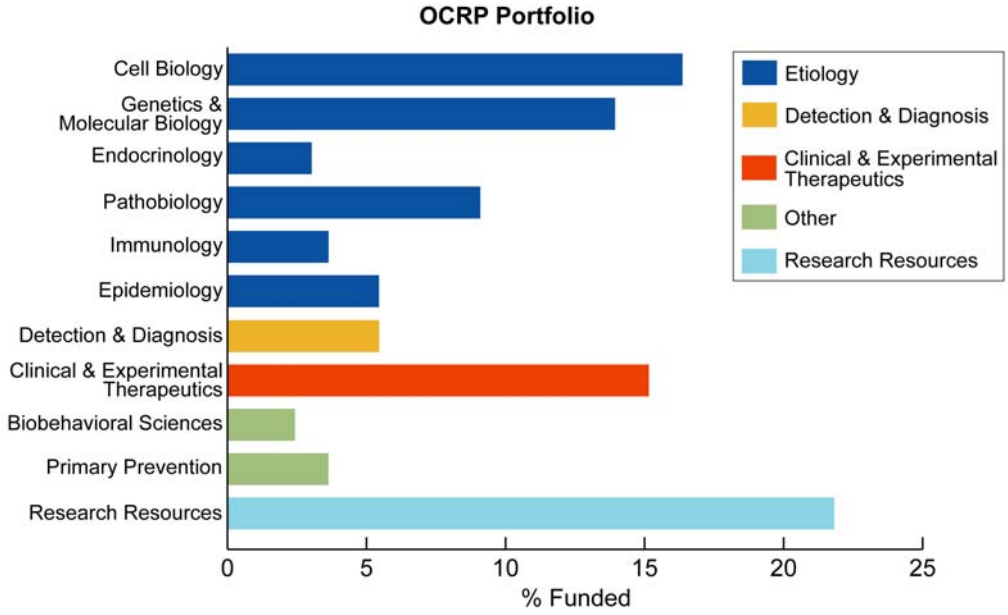
Unique Features of the OCRP

Consumer Advocate Participation

As active members of the OCRP, consumer advocates participate in peer review of proposals as well as in setting program priorities and making funding decisions. Over 70 consumer advocates have served on peer and programmatic review panels for the OCRP since 1997. Consumer advocates' firsthand experience with ovarian cancer provides a unique perspective that is complementary to the expertise of the scientists and clinicians on the panels. Moreover, this perspective helps the scientists understand the human side of how the research will impact the community and allows for funding decisions that reflect the concerns and needs of patients, the clinicians who treat them, and survivors and their families. Equally important, consumer advocates take what they have learned back to their communities. This results in increased awareness of the importance of research and a stronger relationship between the scientific community and the consumer advocate community.

"Being a 13-year survivor of ovarian cancer with two recurrences, chemo, and radiation, I was honored and excited to participate on the DOD Peer Review committee for ovarian cancer. This helped me to fully understand the process of selecting worthy projects to possibly eradicate ovarian cancer and sharing this with other women in my community. It was a wonderful opportunity to meet others from major cancer institutions and see their dedication and impact on this work. As an ovarian cancer advocate, being on the Peer Review committee was interesting, challenging, and worthwhile and added to my advocacy growth. I would highly recommend this experience to others. Hopefully, one day, there will be a cure for ovarian cancer because of these efforts, and this type of work will not be necessary."

Linda Smith, FY05 OCRP Consumer Peer Review Panel Member



Filling Gaps

The OCRP fills important gaps not addressed by other funding agencies in support of ovarian cancer research. The OCRP vision is adapted yearly to facilitate rapid change and to better target funding to the most critical research areas, thus ensuring that the program remains responsive to current needs and future opportunities. A highly flexible management process with proven stewardship, well-qualified people, and productive partnerships is key to the OCRP's success.

As the ovarian cancer research community is small, bringing young investigators into the field is extremely important. Since 1998, the OCRP has funded the best and brightest young ovarian cancer researchers with the New Investigator Award. These investigators have made significant contributions, including testing new therapies for ovarian cancer, discovering new biomarkers that may be used to diagnose the disease in its early stages, and improving the quality of life for women afflicted with the disease. The OCRP investment of $10.1M to support these new investigators resulted in over $85M of subsequent funding as of the end of 2005 to study cancer, including $37M specifically for ovarian cancer research. The New Investigator Award has proven to be a very effective mechanism for attracting and retaining new investigators to ovarian cancer research.

From its inception, one of the main goals of the OCRP was to establish shared resources that could be used to study ovarian cancer. This goal was accomplished by funding 16 Program Project awards to support multidisciplinary programs and build research resources, such as development of animal models specific to ovarian cancer, and establishment of registries and tissue repositories having associated clinical, pathological, and laboratory data. In addition, the Program Project awards have supported nine

investigators new to ovarian cancer. The OCRP investment of $3.86M in these nine researchers has resulted in a tenfold increase in subsequent research dollars, and in 164 research publications in gynecological oncology over the past four years. If these Program Projects were not funded by the OCRP, it is not certain whether these research resources would be available for researchers today. Four recipients of Program Projects - M.D. Anderson Cancer Center, Fred Hutchinson Cancer Research Center, Fox Chase Cancer Research Center, and Brigham and Women's Hospital - were subsequently awarded National Cancer Institute Specialized Program of Research Excellence (SPORE) grants to further support translational research approaches to this disease. The Program Project award has effectively filled the need for critical ovarian cancer research resources and continues to attract young scientists to this field.

OCRP Research Highlights (FY97–Present)

Notable Research Advances

- Showed that vitamin A analogs in combination with progestins stimulate selective apoptosis of ovarian cancer cell lines in vitro
- Generated a chicken model that can be used to study ovarian cancer
- Found that ovarian granulosa cells not only control the menstrual cycle but also control ovarian tumor development
- Discovered epithelial cell adhesion molecule as a possible biomarker for ovarian cancer
- Found that three HOX genes can be used as biomarkers to detect ovarian cancer
- Development of alpha-particle emitters as radiotherapeutics for advanced ovarian cancer
- Showed that squalamine is antiangiogenic and enhances the cytotoxic effect of cisplatin on ovarian cancer cells
- Found that the copper uptake protein CTR1 regulates cellular uptake of platinum drugs, which is important for overcoming drug resistance
- Discovered that poly-l-glutamate conjugated paclitaxel and hyaluronic acid conjugated paclitaxel can be used to overcome paclitaxel resistance

Individual Success Stories

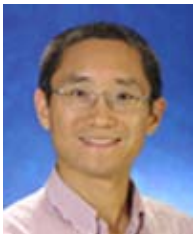
IDEA AND IDEA DEVELOPMENT AWARDS fund independent investigators with innovative ideas for the treatment, detection, diagnosis, or etiology of ovarian cancer.

Dr. Richard Pietras of the University of California at Los Angeles assessed the efficacy of the anti-

angiogenic steroid squalamine in conjunction with cisplatin or carboplatin for ovarian cancer treatment. Treatment with squalamine alone reduced the size of human ovarian cancer xenografts in nude mice, but a combination of squalamine with either cisplatin or carboplatin resulted in a much greater tumor growth inhibition. These preclinical studies led to clinical trials of squalamine. A Phase II trial of squalamine in conjunction with carboplatin for 33 patients with recurrent or refractory ovarian cancer resulted in an objective response in eight of 22 evaluable patients. Squalamine is now in Phase II clinical trials of combination therapies for patients with locally advanced cancers.

- Li D, Williams JI, Pietras RJ. 2002. Squalamine and cisplatin block angiogenesis and growth of human ovarian cancer cells with or without HER-2 gene overexpression. *Oncogene* 21:2805-2814.

Dr. Weiping Zou of the Tulane University Health Science Center investigated the potential angiogenic role in ovarian cancer of dendritic cells (DCs), antigen-presenting cells that play an important role in the immune



system. Tumor angiogenesis is essential for tumor growth and nourishment. Dr. Zou's team isolated the two principal human DC subtypes, plasmacytoid cells (PDCs) and myeloid cells (MDCs), from blood and ovarian tumor ascites and prepared two different Matrigel plugs bearing tumor-associated PDCs and MDCs. They implanted these plugs in healthy non-obese diabetic/severe combined immunodeficient mice and found that tumor-associated PDCs induced angiogenesis through production of tumor necrosis factor-alpha and interleukin-8, while MDCs suppressed angiogenesis through production of interleukin-12. Dr. Zou's research suggests that different DC subsets differentially affect tumor angiogenesis. Understanding the role of these different subsets may lead to novel strategies to treat human ovarian cancer, including blocking PDC-mediated vascularization in tumors.

- Curiel TJ, Cheng P, Mottram P, et al. 2004. Dendritic cell subsets differentially regulate angiogenesis in human ovarian cancer. *Cancer Research* 64:5535-5538.

PROGRAM PROJECT AWARDS establish new multidisciplinary programs in ovarian cancer research by funding *synergistic* programs incorporating two to four research projects and one to two core facilities.

Dr. Samuel Mok from Brigham and Women's Hospital has been seeking new biomarkers to identify early-

stage ovarian cancer. DNA microarray analysis shows that the epithelial cell adhesion molecule (Ep-CAM) is greatly overexpressed in ovarian cancers as compared to normal and benign ovarian epithelia. Ep-CAM autoantibody expression is significantly higher in ovarian cancer patients than in patients with benign tumors or normal controls. Dr. Mok's team also identified kallikrein 6 (hK6, also known as protease M) as being overexpressed in ovarian cancer. Taken together, these findings suggest that hK6 and autoantibodies to Ep-CAM may prove to be valuable serum biomarkers when screening women for early signs of ovarian cancer.

- Kim JH, Herlyn D, Wong KK, et al. 2003. Identification of epithelial cell adhesion molecule autoantibody in patients with ovarian cancer. *Clinical Cancer Research* 9:4782-4791.
- Ni X, Zhang W, Huang KC, et al. 2004. Characterization of human kallikrein 6/protease M expression in ovarian cancer. *British Journal of Cancer* 91:725-731.

Dr. David Bowtell from the Peter MacCallum Cancer Institute in Melbourne, Australia, is directing a large,

multicenter project to study the association among epidemiologic risk factors, low-risk genes, and histologic and novel molecular subtypes of ovarian cancer. To date >1800 cases have been recruited and >1000 fresh frozen tumor samples collected. Expression analysis has been completed on over 200 ovarian cancer cases, providing a dataset to test predictive models. Initial analysis of 55 stage III serous ovarian cancers showed a complex pattern of genomic change with many regions of amplification and loss of heterozygosity in individual tumors. As the sample size increases, changes specific to the platinum-resistant and -responsive groups should be identifiable. In addition, it is expected that common novel regions of DNA copy number change will be identified that can be linked to clinical parameters such as tumor aggressiveness or stage. Dr. Bowtell's group has also identified genetic markers of ovarian cancer risk.

- Webb PM, Hopper JL, Newman B, et al. 2005. Double-strand break repair gene polymorphisms and risk of breast or ovarian cancer. *Cancer Epidemiology Biomarkers & Prevention* 14:319-323.

"In all of my years of serving on a variety of scientific review panels, I have to say the OCRP uniquely drives home to me the urgency of the work to be done. I want to see this disease done with. One woman struck by ovarian cancer is too many for me."

Linda Malkas, Ph.D., FY05 OCRP Peer Review Panel Chair

INSTITUTIONAL TRAINING GRANTS encourage the initiation of a new postgraduate training program in ovarian cancer. The intent of the Institutional Training Grant was to focus on one or more program emphasis area(s) (i.e., etiology, prevention, early detection/diagnosis, and preclinical therapeutics) as related to epithelial ovarian carcinoma and/or primary peritoneal carcinoma.

Dr. Michael Seiden, Chairman of the Research Committee of the Gynecologic Oncology Program at Dana-Farber Cancer Institute/Harvard Cancer Center, directs the Institutional Training Grant funded by the FY02 OCRP. Four postdoctoral scientists funded by this award are mentored by faculty at Dana-Farber/Harvard Cancer Center in the fields of oncogenesis, signal transduction, pathology and mouse models, and cell biology. The first "graduate" of the program, Dr. Ronnie Drapkin, recently accepted a faculty position in the Division of Molecular Pathology at Dana-Farber Cancer Center and received a transition grant from the Ovarian Cancer Research Foundation and a Mentored Clinical Scientist award from the National Cancer Institute. Dr. Seiden has just received a 5-year T32 grant from the National Cancer Institute to provide continuing support to this successful training program.

- Drapkin R, von Horsten HH, Lin Y, et al. 2005. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. *Cancer Research* 65:2162-2169.

NEW INVESTIGATOR AWARDS recognize and support early-career scientists who have innovative ideas for the etiology, detection, diagnosis, or treatment of ovarian cancer.

Dr. Jin Cheng was an assistant professor at the University of South Florida when he received an FY99 New Investigator Award to study the role of the phosphatidylinositol 3-kinase (PI3K)- Akt (protein kinase B) pathway in ovarian cancer. Dr. Chen credits the OCRP award with focusing his research career toward understanding and treating ovarian cancer, research that now constitutes about 80% of his work. In the last 4 years, Dr. Cheng has published 25 articles on cancer research in peer-reviewed journals, including eight on ovarian cancer. An exciting outcome of Dr. Cheng's research has been the "resurrection" of the chemotherapeutic purine analogue triciribine, abandoned about a decade ago because its efficacy was erratic. Dr. Cheng and colleagues showed that triciribine is a specific inhibitor of the Akt signaling pathway and is likely to be effective in the 30% of ovarian cancers exhibiting overexpression of Akt; clinical trials for cancer patients with hyperactive Akt are planned for 2006.

- Yuan ZQ, Feldman RI, Sussman GE, et al. 2003. AKT2 inhibition of cisplatin-induced JNK/p38 and Bax activation by phosphorylation of ASK1: Implication of AKT2 chemoresistance. *Journal of Bioiogical Chemistry* 278:23432-23440.

Dr. Igor Jurisica from the University Health Network in Toronto is creating computational tools and methods for analysis and interpretation of complex and diverse biochemical, biological, and clinical data on epithelial ovarian cancer. The project will be an expansion of the Online Predicted Human Interaction Database, a web-based database of predicted and known human protein-protein interactions. Work thus far has yielded genes differentially expressed between grade I tumors or grade I and II tumors and normal ovarian epithelial cells (OEC) and among grade III and IV tumors and OEC. Dr. Jurisica compared gene expression in patients receiving neoadjuvant versus adjuvant chemotherapy and identified more than 50 genes with differential regulation that might be used to identify responders versus non-responders. These genes are now being validated and functionally studied.

- Kotlyar, M. and I. Jurisica. 2006. Predicting protein-protein interactions by association mining. *Information Systems Frontiers* 8:37-47.

http://cdmrp.army.mil/ocrp